Claims:

1   1.   A transgenic non-human mammal or the progeny thereof having somatic

2 and germline cells which contain, in stably integrated form, a recombinant gene encoding a

3 polypeptide comprising an enzymatically active matrix-degrading enzyme, wherein said

4 recombinant gene is selectively expressed in chondrocytes of said mammal and said

5 expression results in pathological symptoms characteristic of cartilage-degenerative disease.

1   2.   A transgenic animal or the progeny thereof having somatic and germline

2 cells which contain a stably integrated first recombinant gene encoding a polypeptide selected

3 from the group consisting of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-

4 10, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17 and enzymatically active variants

5 thereof.

1   3.   A transgenic animal as defined in claim 2, wherein said first recombinant

2 gene is selectively expressed in synovial chondrocytes of said animal.

1   4.   A transgenic animal as defined in claim 2, wherein said first recombinant

2 gene encodes MMP-13.

1   5.   A transgenic animal as defined in claim 4, wherein said MMP-13 is

2 human.

1   6.   A transgenic animal as defined in claim 4, wherein said first recombinant

2 gene encodes a variant MMP-13 polypeptide comprising enzymatically active proMMP-13.

1   7.   A transgenic animal as defined in claim 6, wherein said recombinant gene

2 comprises a MMP-13-encoding sequence as depicted in SEQ ID NO:1.

1   8.   A transgenic animal as defined in claim 2, wherein said animal is selected

2 from the group consisting of mouse, rat, rabbit, sheep, cow, goat, and pig.

1   9.   A transgenic animal as defined in claim 8, wherein said animal is a mouse.

1   10.   A transgenic animal as defined in claim 2, wherein expression of said

2 recombinant gene is under the control of a first regulatable promoter.

1   11.   A transgenic animal as defined in claim 10, wherein said first regulatable

2 promoter comprises tetO7.

1   12.   A transgenic animal as defined in claim 11, wherein said promoter has the

2 sequence depicted in SEQ ID NO:2.

3   13.   A transgenic animal as defined in claim 10, further comprising a second

4 recombinant gene encoding a polypeptide that regulates said first promoter.

1   14.   A transgenic animal as defined in claim 12, wherein expression of said

2 second recombinant gene is under the control of a second regulatable promoter.

1   15.   A transgenic animal as defined in claim 13, wherein said second

2 regulatable promoter comprises sequences derived from a type II collagen promoter that

3 confer selective expression of said second recombinant gene in joint tissues.

1   16.   A transgenic mouse or the progeny thereof having somatic and germline

2 cells which contain in stably integrated form:

3   (i) a first recombinant gene comprising a sequence encoding a variant MMP-13

4 polypeptide comprising MMP-13*, wherein said sequence is operably linked to a tetO7

5 promoter; and

6   (ii) a second recombinant gene encoding a tTA protein operatively linked to

7 sequences derived from a type II collagen promoter.

1   17.   A transgenic mouse as defined in claim 16 wherein expression of said

2 recombinant genes in joint tissue results in pathological symptoms characteristic of joint

3 degenerative disease.

1   18.   An isolated nucleic acid encoding enzymatically active proMMP-13,

2 wherein said nucleic acid has a sequence selected from the group consisting of the sequence

3 depicted in SEQ ID NO:1, sequence-conservative mutants thereof, and function-conservative

4 mutants thereof.

1   19.   A recombinant cloning vector comprising a nucleic acid as defined in claim

2   18.

1   20.   A host cell comprising a vector as defined in claim 19.

1   21.   A method for producing a polypeptide comprising culturing a cell as

2   defined in claim 20 under conditions appropriate for expression of said enzymatically active

3   proMMP-13.

1   22.   A method for producing phenotypic changes associated with cartilage-

2   degenerative disease in a mammal, comprising maintaining a mammal as defined in claim 1

3   under conditions in which said recombinant gene is selectively expressed in joint tissue of said

4   mammal.

1   23.   A method for producing phenotypic changes associated with cartilage-

2   degenerative disease in a mammal, comprising maintaining a mammal as defined in claim 2

3   under conditions in which said recombinant gene is selectively expressed in joint tissue of said

4   mammal.

1   24.   A method for producing phenotypic changes associated with cartilage-

2   degenerative disease in a mouse, comprising maintaining a mouse as defined in claim 16 for

3   a predetermined time in the absence of tetracycline or biologically active analogues thereof.

1   25.   A method for determining the potential of a composition to counteract

2   cartilage-degenerative disease, said method comprising:

3   (i)   administering a known dose of the composition to a transgenic

4   animal as defined in claim 1 under conditions in which phenotypic indicators associated with

5   cartilage-degenerative disease are expressed;

6   (ii)   monitoring development of the phenotypic indicators of cartilage-

7   degenerative disease for a predetermined time following administration of the composition;

8   and

9   (iii) comparing the extent of the phenotypic indicators in the animal to

10   which the composition was administered relative to a control transgenic animal that had not

11   been exposed to the composition,

12   wherein any difference in the nature or extent of the phenotypic indicators, or any difference

13   in the time required for the phenotypic indicators to develop, indicates the potential of the

14   composition to counteract cartilage-degenerative disease.

1   26.   A method for determining the potential of a composition to counteract

2   cartilage-degenerative disease, said method comprising:

3   (i)   maintaining a transgenic animal as defined in claim 16 for a

4   predetermined time in the absence of tetracycline or a tetracycline analogue, wherein said

5   maintainence results in the appearance of one or more phenotypic indicators of cartilage-

6   degenerative disease in said animal;

7   (ii)   administering a known dose of said composition to the animal;

8   (iii) monitoring development of said phenotypic indicators for a

9 predetermined time following administration of the composition; and

10   (iii) comparing the extent of the phenotypic indicators in the animal to

11 which the composition was administered relative to a control transgenic animal that had not

12 been exposed to the composition,

13 wherein any difference in the nature or extent of the phenotypic indicators indicates the

14 potential of the composition to counteract cartilage-degenerative disease.

1   27. A method for determining the potential of a composition to counteract

2 cartilage-degenerative disease, said method comprising:

3   (i) providing a transgenic animal as defined in claim 16 that had been

4 maintained in the presence of tetracycline or a tetracycline analogue to repress expression of

5 said first recombinant gene;

6   (ii) substantially simultaneously (a) administering to said animal a

7 known dose of said composition and (b) withdrawing said tetracycline;

8   (iii) monitoring development of phenotypic indicators of cartilage-

9 degenerative disease for a predetermined time following administration of the composition;

10 and

11   (iv) comparing the extent of the phenotypic indicators in the animal to

12 which the composition was administered relative to a control transgenic animal that had not

13 been exposed to the composition,

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14   wherein any difference in the nature or extent of the indicators, or any difference in the time

15   required for the indicators to develop, indicates the potential of the composition to counteract

16   cartilage-degenerative disease.

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